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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/746,662 | 12/22/2000 | Lechoslaw Turski | 102286-123 | 1433 |

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| EXAMINER |
|---|
| LI, RUIXIANG |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | |

DATE MAILED: 09/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Advisory Action | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/746,662 | TURSKI ET AL. | |
| | Examiner | Art Unit | |
| | Ruixiang Li | 1646 | |

*--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

THE REPLY FILED 08 September 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *09/08/2003*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *21-25,29,30 and 38*.

   Claim(s) withdrawn from consideration: *26-28*.

8. ☐ The proposed drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)( PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Continuation of 5. does NOT place the application in condition for allowance for the following reasons:

(i) The rejection of claims 21, 22, 24, and 25 under 35 U.S.C. 103(a) as being unpatentable over Shishikura et al. (U.S. Patent No.6,133,258) in view of Csuzdi et al. (WO 97/28163) remains.

Applicants argue that, as explained in Dr. Smith's Declaration, Drs. Smith and Turski were the first to recognize the glutamate ionotropic AMPA receptor as a target for the treatment of demyelinating disorders and that Shishikura et al. do not disclose or suggest the use of an AMPA receptor inhibitor for treating disorders induced by demyelination. Applicants' argument has been fully considered, but is not deemed to be persuasive because the inventor's work was published in Nature Medicine in 2000, which is after 102 (e) date of U. S. Patent No. 6,133,258 by Shishikura et al. As a matter of fact, Shishikura et al. teach a method of treating multiple sclerosis, which is a demyelinating disorder, with an AMPA receptor antagonist (pyridothiazine derivatives; see, e.g., claims 7-9). Thus, Dr. Smith's declaration is insufficent to overcome the rejection.

Applicants argue that Csuzdi et al. do not discuss demyelinating disorders, and there is no teaching or suggestion that the disclosed 2,3-benzodiazepine derivatives could be used to treat demyelinating disorders. Thus, Shishikura et al. and Csuzdi et al., alone or in combination, do not teach or suggest the claimed methods of treating demyelinating disorders by administering inhibitors of the interaction of glutamate with the AMPAreceptor complex. Applicants' argument has been fully considered, but is not deemed to be persuasive because Shishikura et al. teach a method of treating a demyelinating disorder, multiple sclerosis with an AMPA receptor antagonist and Csuzdi et al. teach 2,3-benzodiazepine derivatives, including amino- or desamino-2,3-benzodiazepine, and their use as AMPA receptor non-competitive inhibitors for treating neurological disorders. Therefore, it would have been obvious to an artisan at the time the invention was made to treat multiple sclerosis by administering an AMPA receptor inhibitor, e.g., amino- or desamino-2,3-benzodiazepine taught by Csuzdi et al. with a reasonable expectation of success. One would have been motivated to do so because Shishikura et al. teach that an AMPA receptor antagonist is useful for treating multiple sclerosis, a demyelinating disorder.

(ii) The rejection of claims 23, 29, 30, and 38 under 35 U.S.C. 103(a) as being unpatentable over Shishikura et al. (U.S. Patent No.6,133,258) in view of Csuzdi et al. (WO 97/28163), and further in view of Prineas et al. (Demyelinating Diseases, in Greenfield's Neuropathology, Chapter 13, pages 813-896, 1997) also remains.

Applicants argue that, as discussed in the declaration of Dr. Smith, the combined disclosures of Shishikura et al., Csuzdi et al., and Prineas teach one of ordinary skill in the art that AMPA receptor inhibitors can be used to treat neurodegerative disorders. These references do not teach or suggest the treatment of demyelinating diseases generally, or secondary demyelinating disorders in particular. Applicants further submit that there would no no motivation to combine the teachings of the cited references because they are directed to distinct subject area. Applicants' argument has been fully considered, but is not deemed to be persuasive for the reasons set forth above. In addition, since Prineas et al. teach that interferon-beta curtails immune activation by counteracting some of the proinflammatory actions of interferon-gamma and reduces the rate of clinical relapses of multiple sclerosis and the general pathological features of demyelinating disorders. Therefore, it would have been obvious to an artisan at the time the invention was made to treat multiple sclerosis by administering a pharmaceutical composition comprising an AMPA receptor antagonist taught by Shishikura et al. in combination with interferon-beta or to treat the specific secondary demyelinating disorders listed in claim 23 with a reasonable expectation of success. One would have been motivated to do so because both an AMPA receptor antagonist and interferon-beta are beneficial for the treatment of multiple sclerosis and an artisan would reasonably expect the combination of the two compounds to be beneficial for the same purpose, i.e., treating multiple sclerosis and because Shishikura et al. teach that an AMPA receptor antagonist is beneficial for treating an demyelinating disorder (multiple sclerosis) and an artisan would reasonably expect the treatment with an AMPA receptor antagonist to be beneficial for treating a different type of demyelinating disorder, such as a secondary demyelinating disorder listed in claim 23.

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